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Date: March 7, 2005

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Company: U.S. PTO **Phone:** (571) 272-0655 ☐ Notify recipient before sending

From: Shirley Chen, Ph.D. **Phone:** (650) 565-3856 **Return Fax:** (650) 493-6811

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[727] Pentostatin, Tacrolimus, and "Mini"-Methotrexate for Graft-Versus-Host Disease (GVHD) Prophylaxis: A Phase I/II Controlled, Randomized Study. Session Type: Oral Session

M. de Lima, D. Couriel, M. Munsell, M. Westmoreland, H. Shah, J. deJesus, C. Hosing, S. Ghosh, P. Anderlini, J. Gajewski, B. Andersson, S. Kornblau, B. Hocking, C. Ippoliti, S. Giralt, E. Shpall, R. Champlin. Department of Blood and Marrow Transplantation, M.D. Anderson Cancer Center, Houston, TX, USA

GVHD remains a major obstacle to a successful unrelated (UD) or mismatched related (MRD) donor hematopoietic stem cell transplantation (HSCT). Pentostatin is a purine nucleoside analog that targets adenosine deaminase and leads to lymphocyte depletion, with low potential for myelosuppression. We are investigating the incorporation of pentostatin to our standard GVHD prophylaxis regimen with tacrolimus (tacro) and methotrexate (MTX).
Methods: This is an adaptive randomized, dose finding study that takes into account toxicity and efficacy in a Baysean "play the winner" design. The "winner" dose moves to the phase II portion of the study. Probability of assignment to the control group was fixed at 20%. Recipients of UD and MRD are eligible; all analysis is done by intention to treat. Success was defined as being alive, engrafted, in complete remission(CR), without GVHD at study completion (100 days post HSCT). Development of grade III-IV acute (a) GVHD defined failure at any time, while grade I-II did not constitute failure if absent by day 100.This design has power 0.7 to detect a dose that has a success rate of 60% for low-risk patients (HLA matched, in CR) and 45% for high-risk patients (mismatched, not in CR). High-resolution typing was available for all donor-recipient pairs at HLA-DRB1 and -DQB1 loci, and to 83% of the pairs at HLA-A and –B loci; all patients had low-resolution –C typing. Treatment plan: tacro from day –2 (target level of 5-15 ng/ml) and MTX 5 mg/m^2 on days +1, +3, +6 to all patients; day +11 was given only to the control group. Pentostatin was given on days +8, +15, +22 and +30, in treatment arms: 0.5 mg/m^2, 1 mg/m^2, 1.5 mg/m^2, and 2 mg/m^2.
Results: 73 patients, median age 45 yrs (range 18-72) have been enrolled. Diagnosis were AML/MDS(n=48), ALL(n=8), CML (n=10) and NHL(n=7); 58% of the patients were not in CR at HSCT. Conditioning regimens were busulfan based(n=52), melphalan based(n=10), BEAM(n= 2), and CyTBI(n =9); 71% were ablative and 29%, reduced intensity. ATG was used in the regimen in 86% of the cases. Stem cell source: bone marrow (n=67) and peripheral blood(n=6). Donors: UD(n=67) and MRD(n=6). Proportion of patients with donor-recipient HLA mismatches was 24%, 20%, 33%, 21% and 40%, respectively for the 5 study arms; median age was similar. 85% of the intended pentostatin doses were delivered. Pentostatin did not delay engraftment. Incidence of toxicities (control vs. study arms): renal (all grade I/II)=47% vs 36%; TTP/HUS= 12% vs 9% (more severe among pentostatin patients); early relapse= 12% vs 5%; engraftment failure=6% vs 3%; delayed engraftment (>21 days): 0 vs. 5%. Probability that dose 1.5 mg/m^2 is better than control is 0.9341.

Pentostatin dose	control group (n=17)	0.5 mg/m² (n=10)	1 mg/m² (n=12)	1.5 mg/m² (n=24)	2 mg/m² (n=10)
gd II-IV aGVHD	47%	44%	63%	29%	50%
gd III-IV aGVHD	20%	33%	27%	10%	10%
CMV reactivation	41%	30%	33%	50%	50%
bact/fungal infection	59% / 12%	60% / 10%	50% / 18%	55% / 17%	70% / 10%
Not evaluable	n=2	n=1	n=1	n=4	n=0
Failure rate	47%	70%	33%	29%	40%

Conclusions: This preliminary analysis indicates that aGVHD rate may be reduced with pentostatin 1.5 mg/m^2, without interference with engraftment. Longer follow-up and larger number of patients will be needed to assess impact on survival.
Abstract #727 appears in Blood, Volume 104, Issue 11, November 16, 2004
Keywords: Unrelated donor stem cell transplant|Graft-versus-host disease (GVHD)|Pentostatin

Tuesday, December 7, 2004, 8:00 AM

Simultaneous Session: GvHD and Immune Reconstitution after Transplantation (8:00 AM-10:00 AM)